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Clinical and Economic Benefits of Fidaxomicin Compared to Vancomycin for *Clostridium difficile* Infection

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We studied the clinical and economic impact of a protocol encouraging the use of fidaxomicin as a first-line drug for treatment of *Clostridium difficile* infection (CDI) in patients hospitalized during a 2-year period. This study evaluated patients who received oral vancomycin or fidaxomicin for the treatment of CDI during a 2-year period. All included patients were eligible for administration of fidaxomicin via a protocol that encouraged its use for selected patients. The primary clinical endpoint was 90-day readmission with a diagnosis of CDI. Hospital charges and insurance reimbursements for readmissions were calculated along with the cost of CDI therapy to estimate the financial impact of the choice of therapy. Recurrences were seen in 10/49 (20.4%) fidaxomicin patients and 19/46 (41.3%) vancomycin patients ($P = 0.027$). In a multivariate analysis that included determinations of severity of CDI, serum creatinine increases, and concomitant antibiotic use, only fidaxomicin was significantly associated with decreased recurrence (adjusted odds ratio [aOR], 0.33; 95% confidence interval [CI], 0.12 to 0.93). The total lengths of stay of readmitted patients were 183 days for vancomycin and 87 days for fidaxomicin, with costs of $454,800 and $196,200, respectively. Readmissions for CDI were reimbursed on the basis of the severity of CDI, totaling $151,136 for vancomycin and $107,176 for fidaxomicin. Fidaxomicin drug costs totaled $62,112, and vancomycin drug costs were $6,646. We calculated that the hospital lost an average of $3,286 per fidaxomicin-treated patient and $6,333 per vancomycin-treated patient, thus saving $3,047 per patient with fidaxomicin. Fidaxomicin use for CDI treatment prevented readmission and decreased hospital costs compared to use of oral vancomycin.

Clostridium difficile infection (CDI) has been increasing in both severity and incidence (1, 2). In 2011, it was associated with an estimated 29,000 deaths in the United States alone (1). The current mainstays of therapy, metronidazole and oral vancomycin, have been used in CDI therapy for over 30 years with very little drug resistance seen (3). Current guidelines for the treatment of CDI recommend metronidazole for mild to moderate infection and vancomycin for severe infection or recurrent episodes (3, 4). Recent data have challenged the positioning of these drugs for CDI therapy, as oral vancomycin was superior to metronidazole in a study comparing the two drugs and tolevamer, a toxin-binding agent that did not fair well in the study (5).

Recently, fidaxomicin, a nonabsorbed macrolide antibiotic, was studied for the treatment of CDI and was found to be superior to oral vancomycin for the prevention of recurrences of CDI (6, 7). Cost concerns and a lack of updated guidelines for CDI may have prevented uptake of fidaxomicin by hospital and managed-care formularies, decreasing its utilization. However, CDI treatment is itself expensive, and if the use of fidaxomicin could prevent readmissions, it is possible that the increased clinical benefits would correlate with decreased costs. To achieve these ends, we instituted a guideline that recommended fidaxomicin as a first-line agent for treatment of many patients with CDI. This study evaluated the outcomes, costs, and costs avoided associated with the use of vancomycin and fidaxomicin after the implementation of this policy.

MATERIALS AND METHODS

This was a single-center retrospective study of adult patients who received oral vancomycin or fidaxomicin for CDI treatment from January 2012 to January 2014. A protocol was established encouraging fidaxomicin use for selected patients (Fig. 1). All patients included in this study were eligible for fidaxomicin therapy by the terms of the protocol. The dose recommended by the protocol was 200 mg administered orally twice daily.

Inclusion criteria for the study were age of ≥18 years, acute diarrhea, and a positive assay result for *C. difficile*. The laboratory assayed all suspected CDI patients for glutamate dehydrogenase and toxin production. If results were inconclusive, a loop-mediated isothermal amplification (LAMP) assay was performed for confirmation. Patients whose initial therapy had failed to cure them were excluded as were those who received any CDI therapy prior to receiving vancomycin or fidaxomicin. Patients who had changed from vancomycin to fidaxomicin therapy were counted as vancomycin failures and excluded from the study. The severity of CDI episodes was assessed on the basis of criteria defined in published guidelines (3). Concomitant antibiotics were defined as any use of 2 or more doses of antibacterial agents during the course of CDI.

The primary endpoint was 90-day readmission with a diagnosis of CDI. Secondary goals were to determine costs attributable to length of stay with CDI recurrences that required readmission. Patients were identified using data in QualityAdvisor (Premier Inc., Charlotte, NC), which was also used to identify patients for readmission and to calculate the costs of readmissions.

To assess the financial impact of CDI, we used Medicare reimbursement values for the hospital of $6,739 for a case of CDI without compli-

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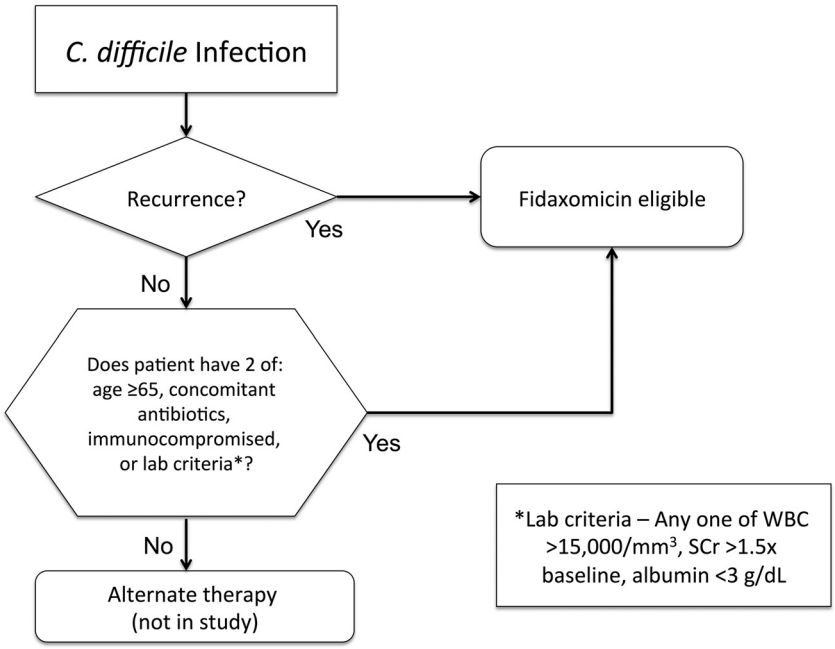

FIG 1 Protocol for fidaxomicin eligibility. WBC, white blood count; SCr, serum creatinine.

cations or comorbidities (CC), $9,385 for CDI cases with CC, and $14,701 for CDI cases with major CC. We estimated pharmacy drug costs associated with fidaxomicin to be $92/dose and those associated with vancomycin to be $5.16/dose. The cost of hospitalization associated with readmission was calculated on the basis of actual hospital-day costs. Reimbursement for CDI was based on Medicare reimbursement per disease severity for each case and was subtracted from these figures to determine the loss associated with readmission.

Data were analyzed by chi-square or *t* test as appropriate. Logistic regression was performed with 90-day readmission for CDI as a binary variable to determine characteristics associated with readmission. Variables that had a *P* value of <0.1 were entered into the multivariate model. A *P* value of ≤ 0.05 was chosen to indicate statistical significance. Statistical analyses were performed using Stata 13.0 (College Station, TX). The Institutional Review Board of the AtlanticCare Regional Medical Center approved the protocol.

RESULTS

During the study period, 46 patients received oral vancomycin and 49 received fidaxomicin. Patient characteristics and study results are listed in Table 1 and Table 2, respectively. Subjects in both groups were generally elderly patients who had been in the hospital for over 1 week. Most patients had moderate to severe CDI (23/46 [50%] vancomycin patients, 34/49 [69.4%] fidaxomicin patients, $P = 0.054$). Significantly more patients in the fidaxomicin group were treated for a recurrent CDI (22/46 [47.8%] vancomycin versus 38/49 [77.6%] fidaxomicin, $P = 0.003$). Nonsignificant differences were seen in concomitant antibiotic use (14/46 [30.4%] vancomycin versus 24/49 [49%] fidaxomicin, $P = 0.065$) and serum creatinine levels of $>1.5\times$ baseline (9/46 [19.6%] vancomycin versus 18/49 [36.7%] fidaxomicin, $P = 0.064$). LAMP testing was used to confirm the diagnosis of CDI in 10/46 (21.7%) of vancomycin patients and 13/49 (26.5%) of fidaxomicin patients ($P = 0.59$). All fidaxomicin patients received 200 mg twice daily; vancomycin patients received 125 to 250 mg four times daily.

Significantly fewer patients were readmitted with CDI within 90 days in the fidaxomicin group than in the vancomycin group (10/49 [20.4%] versus 19/46 [41.3%], respectively, $P = 0.027$). In a multivariate analysis that included fidaxomicin use, severity of CDI, serum creatinine increase of $1.5\times$ baseline, and concomitant

TABLE 1 Patient characteristics[a]

Patient characteristic	Values for patients treated with:		*P* value
	Oral vancomycin ($n = 46$)	Fidaxomicin ($n = 49$)	
Age (yrs)	72.1 ± 10.1	73.2 ± 11.9	0.64
LOS (days)	10.6 ± 7.42	8.96 ± 7.25	0.26
ICU at diagnosis	9 (19.6)	13 (26.5)	0.42
Current CDI episode was recurrence	22 (47.8)	38 (77.6)	0.008
Concomitant antibiotics	14 (30.4)	24 (49)	0.065
Moderate or severe CDI	23 (50)	34 (69.4)	0.054
Creatinine $>$ 1.5× baseline	9 (19.6)	18 (36.7)	0.064
Readmission with CDI within 90 days	19 (41.3)	10 (20.4)	0.027

[a] With the exception of the *P* values, data are presented as mean ± standard deviation or *n* (percent). LOS, length of stay; ICU, intensive care unit; CDI, *Clostridium difficile* infection.

TABLE 2 Multivariate analysis

Variable	Adjusted odds ratio (95% confidence interval)	*P* value
Fidaxomicin	0.33 (0.12–0.93)	0.036
Severe CDI	1.54 (0.78–3.04)	0.217
Creatinine > 1.5× baseline	0.34 (0.10–1.14)	0.080
Concomitant antibiotics	1.14 (0.14–3.17)	0.796

antibiotic use, only fidaxomicin use was associated with a significantly lower risk of 90-day recurrence (adjusted odds ratio [aOR], 0.33; 95% confidence interval [CI], 0.12 to 0.93; $P = 0.036$). Among the patients who were experiencing their first episode of CDI, 11/24 (45.8%) who received vancomycin and 0/11 (0%) who received fidaxomicin had readmissions within 90 days ($P = 0.007$). Among patients who were being treated for a second episode or for an episode beyond the second, recurrence rates were 8/22 (36.4%) and 10/38 (26.3%) in patients treated with vancomycin and fidaxomicin, respectively ($P = 0.413$).

Fidaxomicin drug costs totaled $62,112, and vancomycin costs were $6,646. Readmissions for CDI were reimbursed on the basis of the severity of CDI, and reimbursements totaled $151,136 for vancomycin and $107,176 for fidaxomicin. The total lengths of stay for the readmitted patients were 183 days for the vancomycin group and 87 days for the fidaxomicin group, as determined on the basis of actual costs of $454,800 and $196,200, respectively. Thus, we calculated that fidaxomicin was associated with $142,507 in cost savings even though 3 more patients were in the fidaxomicin group. Analyzed on the basis of the costs of drug, costs of readmission, and readmission reimbursement, the hospital lost an average of $3,286 per fidaxomicin-treated patient and $6,333 per vancomycin-treated patient. Thus, fidaxomicin use saved $3,047 per patient.

DISCUSSION

The treatment pathway for CDI has been fairly thoroughly defined for many years. Recent studies have eroded the evidence base for the prominence in therapy of metronidazole and vancomycin. It is logical to presume that the lessened impact of fidaxomicin on the human microbiome is responsible for its better efficacy in preventing recurrences of CDI compared to vancomycin, though this has not been definitely established (8).

Fidaxomicin is expensive, and it is likely that its significantly higher pharmacy cost has led to decreased utilization compared to what its utilization would have been if it were priced lower. While a new-technology add-on payment (NTAP) for fidaxomicin was granted by the Centers for Medicare and Medicaid Services (CMS) to help defray acquisition costs (9), it may not completely cover the increased cost of fidaxomicin for patients admitted for a hospital stay of more than a few days. Also, it is possible that "budget silos" in hospitals prevent the increased reimbursement from reaching the pharmacy budget, decreasing the incentive for pharmacy departments to encourage fidaxomicin use when oral vancomycin is almost free.

In our cohort, fidaxomicin was associated with approximately 50% fewer recurrences of CDI within 90 days than vancomycin in a population that was "preapproved" for either drug. This result is particularly noteworthy since the patients who were received fidaxomicin were more likely to be experiencing recurrent infections, which are often associated with further recurrences (10, 11). The patients who received fidaxomicin also had other surrogate measures of increased illness that trended toward significance, including elevations in serum creatinine levels and concomitant antibiotic use. While not definitive, this suggests that clinicians preferred fidaxomicin use for patients who were more ill, and yet fidaxomicin was still associated with positive outcomes. However, it should be noted that, in our study, no significant difference was seen between groups for patients who had already had a recurrence of CDI. In a multivariate analysis that was performed to consider other factors, the association between fidaxomicin and decreased recurrence was strengthened. By preventing recurrences, fidaxomicin use saved the hospital approximately $142,507. This helped to validate the fidaxomicin protocol and justify the increased acquisition costs of the drug.

Our study had limitations. We were able to track only those patients who were readmitted into the same health care system as that used for treatment of their initial infection, and it is possible that we missed patients with recurrent infection who were treated as outpatients or at other institutions. However, this limitation would have been the case for both groups and its effect would be unpredictable. Our study was also relatively small, and while the results were significant, a larger study would provide more robust evidence. *C. difficile* was not cultured, and strain typing was not performed, so we were not able to evaluate the impact of this factor on outcomes.

Conclusion. A pathway that encouraged fidaxomicin use for CDI was associated with both decreased readmissions within 90 days and cost savings. Considering costs beyond the pharmacy budget, fidaxomicin use may be cost effective compared with vancomycin use for CDI therapy.

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Bhagyashri Navalkele, Gemma Downham, Kevin Haynes, and Manish Trivedi declare that we have no conflicts of interest.

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